ORGANIC LETTERS

2006
Vol. 8, No. 1
175−177

Claisen-Type Condensation of Vinylogous Acyl Triflates

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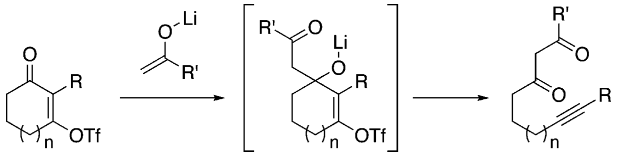
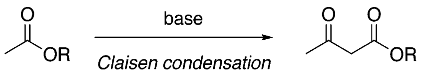
Received November 16, 2005

ABSTRACT



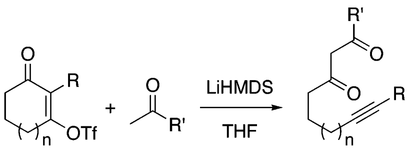
The Claisen-type condensation reaction of cyclic vinylogous carboxylic acid triflates with lithium enolates and their analogues produces acyclic alkynes bearing a 1,3-diketone-type moiety. The present transformation is proposed to proceed via a 1,2-addition of the enolate to the vinylogous acyl triflate, followed by fragmentation of the aldolate intermediate.

The Claisen condensation is one of the hallmark reactions of organic chemistry.[1] The first report on the Claisen condensation dates back more than a century and describes the homocoupling reaction of esters in the presence of an excess amount of base to yield 1,3-ketoesters (eq 1). This mechanistic pathway extends to the cross-coupling reactions of esters with a variety of enolates and enolate analogues.



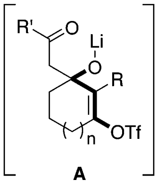
(1)

During the course of our investigations on the reaction between cyclic vinylogous acyl triflates (**1**) and organolithium reagents,[2] we found that the cross-coupling reaction of **1** with lithium enolates derived from **2** proceeds to give **3**, β-dicarbonyls tethered to alkynes (eq 2). This reaction appears to be a direct mechanistic analogue of the Claisen condensation using a vinylogous carboxylic acid ester as a starting material.



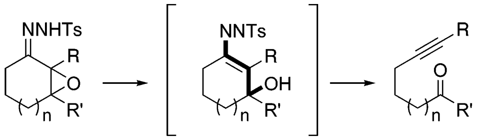
1 **2** **3**

(2)



A

The fragmentation event also calls to mind the process developed by Eschenmoser and Tanabe (eq 3),[3,4] although the reaction protocols are distinctly different (vide infra).



(3)

Eschenmoser-Tanabe fragmentation

Herein, we report a Claisen-type condensation of vinylogous acyl triflates, which appears to proceed via a fragmentation pathway and is, to the best of our knowledge, unprecedented.

We chose triflate **1a** ($R = Me$, $n = 1$ in eq 2) and the lithium enolate of acetophenone (**2a**, $R' = Ph$ in eq 2) as

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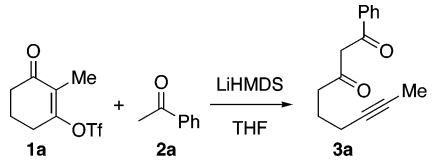
[1] For reviews on the Claisen condensation, see: (a) Davis, B. R.; Garratt, P. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 795−863. (b) Hauser, C. R.; Hudson, D. E. *Org. React.* **1942**, *1*, 266. (c) Hauser, C. R.; Swamer, F. W.; Adams, J. T. *Org. React.* **1954**, *8*, 59. For a review on the Dieckman condensation, see: (d) Schaefer, J. P.; Bloomfield, J. J. *Org. React.* **1967**, *15*, 1.

[2] (a) Kamijo, S.; Dudley, G. B. *J. Am. Chem. Soc.* **2005**, *127*, 5028.

10.1021/ol0527781 CCC: $33.50

Table 1. Claisen-Type Condensation of the Vinylogous Acyl Triflate **1a** with Nucleophilic Derivatives of **2a**[a]

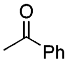
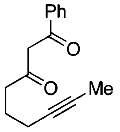
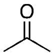
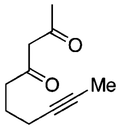
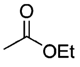
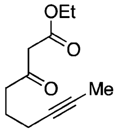
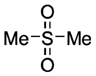
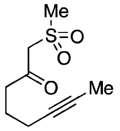
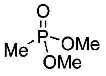
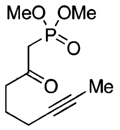


entry	triflate **1a**, equiv	acetophenone **2a**, equiv	LiHMDS, equiv	yield, %[b]
1	1.0	1.4	1.2	56[c]
2	1.0	2.4	2.2	85[d]
3	1.0	1.2	2.2	70

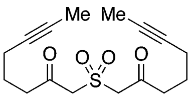
[a] The triflate **1a** was reacted with acetophenone **2a** (pretreated with LiHMDS) in THF at −78 to 60 °C within 80 min. [b] ^{1}H NMR yield using anisole as an internal standard unless otherwise noted. [c] The recovery of **1a** was observed. [d] Isolated yield.

the prototype, and we screened to find optimal conditions for the formation of the acyclic alkynyl-1,3-diketone **3a**. The reaction stoichiometry had a significant effect on the yield of **3a** (Table 1). The reaction of triflate **1a** with 1.4 equiv of **2a** and 1.2 equiv of LiHMDS (lithium hexamethyldisilazide) gave **3a** in 56% yield along with recovered **1a** (entry 1). Treatment of **1a** with 2.4 equiv of **2a** and 2.2 equiv of LiHMDS furnished the product (**3a**) in 85% isolated yield (entry 2). When **1a** was treated with 1.2 equiv of **2a** and 2.2 equiv of LiHMDS, **3a** was obtained in 70% yield (entry 3). This stoichiometric requirement is consistent with the traditional Claisen condensation, wherein the relatively acidic dicarbonyl product consumes 1 equiv of base as it is formed.

Table 2. Claisen-Type Condensation of the Vinylogous Acyl Triflate **1a** with Nucleophilic Derivatives[a]

entry	pre-nucleophile (analogue of **2**)	product (analogue of **3**)	**3**	yield, %[b]
1	 **2a**		**3a**	85
2	 **2b**		**3b**	42
3	 **2c**		**3c**	88
4[c]	 **2d**		**3d**	53[d]
5[c]	 **2e**		**3e**	21

[a] Triflate **1a** (0.5 mmol) was reacted with the pre-nucleophile (1.2 mmol, pretreated with 1.1 mmol of LiHMDS) in 2 mL of THF at −78 to 60 °C within 80 min. [b] Isolated yield. [c] *n*-BuLi was used instead of LiHMDS. [d] Diyne **3d′** was obtained in 8.4% yield.

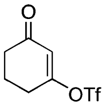
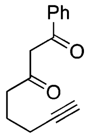
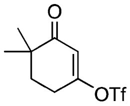
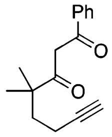
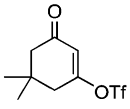
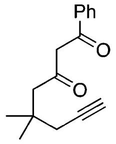
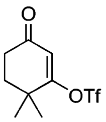
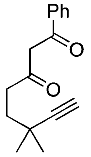
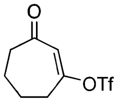
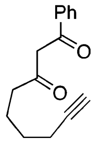


3d'

We next examined the Claisen-type condensation of the vinylogous acyl triflate **1a** with various nucleophiles derived from analogues of **2** (Table 2). As mentioned above, the reaction between triflate **1a** and acetophenone (**2a**, pretreated with LiHMDS) in THF afforded acyclic alkynyl-1,3-diketone **3a**[5] in 85% yield (entry 1). The lithium enolate derived from acetone gave diketone **3b** in moderate yield (entry 2). The ethyl acetate enolate produced ketoester **3c** in 88% yield (entry 3). The anion of dimethyl sulfone (**2d**) reacted with **1a** to furnish β-ketosulfone **3d** in moderate yield (entry 4), along with a small amount of the diyne **3d′**. A similar reaction using dimethyl methylphosphonate (**2e**) provided β-ketophosphonate **3e** in low yield (entry 5).

We then explored the Claisen-type condensation using various triflates **1** and the lithium enolate of acetophenone (Table 3). Triflate **1b** afforded the corresponding diketone

Table 3. Claisen-Type Condensation of Triflates **1** with Acetophenone[a]

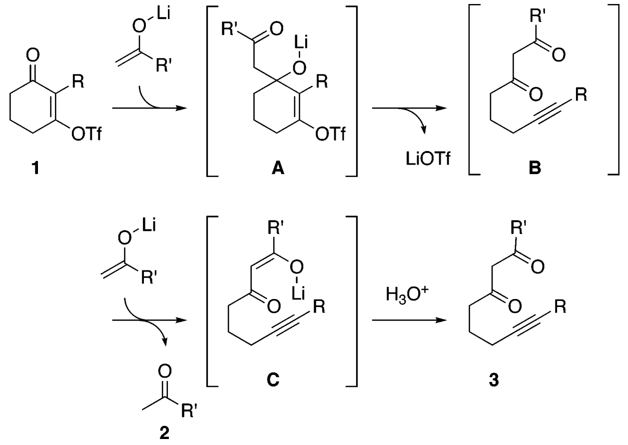
entry	triflate	**1**	product	**3**	yield, %[b]
1		**1b**		**3f**	95
2		**1c**		**3g**	–[c]
3		**1d**		**3h**	45
4		**1e**		**3i**	79
5		**1f**		**3j**	90

[a] Triflate **1** (0.5 mmol) was reacted with acetophenone (**2a**, 1.2 mmol, pretreated with 1.1 mmol of LiHMDS) in 2 mL of THF at −78 to 60 °C within 80 min. [b] Isolated yield. [c] Decomposition of **1c**.

3f in excellent yield (entry 1). The six-membered triflates **1c**−**e** bearing a geminal dimethyl group were next examined. The reaction of triflate **1c**, which bears a sterically congested quaternary center α to the carbonyl group, resulted in decomposition; no desired product (**3g**) was obtained (entry 2). On the other hand, the triflates such as **1d** and **1e**, in which the carbonyl groups are progressively less hindered, furnished the corresponding products **3h** and **3i** in 45% and 80% yield, respectively (entries 3 and 4). Accordingly, the reaction seemed to be sensitive to the steric demands of the substrates.[6] The seven-membered triflate **1f** gave the desired product **3j** in high yield (entry 5).

The mechanistic pathway for this novel Claisen-type condensation of vinylogous acyl triflates **1** with lithium enolates generated from **2** is proposed as shown in Scheme 1. Initially, 1,2-addition of the lithium enolate to the carbonyl group of triflate **1** generates intermediate **A**. Steric congestion around the reacting site would retard this addition process, and the prolonged exposure of triflate **1** to the reaction conditions would lead to its decomposition. The Grob-type fragmentation effects C−C bond cleavage along with extrusion of LiOTf to give intermediate **B**.[2] Subsequently, a second equivalent of the enolate abstracts a proton from the newly formed active methylene moiety to furnish intermediate **C**, which yields **3** upon aqueous workup.[7]

Scheme 1. Proposed Mechanistic Pathway for the Claisen-Type Condensation of Vinylogous Acyl Triflates **1** with Lithium Enolates



In summary, we describe the first examples of the Claisen-type condensation reaction of vinylogous acyl triflates (**1**) with lithium enolates and their analogues to form acyclic alkynes bearing a 1,3-diketone-type moiety (**3**). The present transformation contains an intriguing C−C bond cleavage process initiated by the nucleophilic addition of the lithium enolates to the carbonyl group of triflates **1**.

Acknowledgment. This research was supported by a grant from the James and Ester King Biomedical Research Program, Florida Department of Health, an award from Research Corporation, and by the FSU Department of Chemistry and Biochemistry. S.K. is a recipient of the Postdoctoral Fellowship for Research Abroad (2004) from the Japan Society for the Promotion of Science (JSPS). We thank all of these agencies for their support. We thank Dr. Joseph Vaughn for assistance with the NMR facilities, Dr. Umesh Goli for providing the mass spectrometry data, and the Krafft Lab for access to their FT-IR instrument.

Supporting Information Available: Experimental procedures, characterization data for products **3**, and details of a deuterium-labeling experiment in support of the mechanism proposed in Scheme 1. This material is available free of charge via the Internet at http://pub.acs.org.

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(3) (a) Eschenmoser, A.; Felix, D.; Ohloff, G. *Helv. Chim. Acta* **1967**, *50*, 708. (b) Felix, D.; Shreiber, J.; Ohloff, G.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 2896. (c) Tanabe, M.; Crowe, D. F.; Dehn, R. L. *Tetrahedron Lett.* **1967**, 3943. (d) Tanabe, M.; Crowe, D. F.; Dehn, R. L.; Detre, G. *Tetrahedron Lett.* **1967**, 3739.

(4) (a) Grob, C. A.; Schiess, P. W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 1. (b) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535. (c) Wharton, P. S.; Hiegel, G. A. *J. Org. Chem.* **1965**, *30*, 3254. (d) Weyerstahl, P.; Marschall, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, pp 1041−1070.

(5) 1,3-Diketones **3a**, **3b**, **3f**, and **3h**−**k** exist predominantly in the enol form in $CDCl_3$. See Supporting Information for details.

(6) The reactions of enolates derived from more hindered esters such as ethyl valerate and ethyl isobutyrate with triflate **1a** did not proceed well. In the former case, we could detect the corresponding product in the crude mixture by mass spectrometry (ESI, $C_{14}H_{22}0_3Na$; $M^+ = 261.1$); however, the yield was quite low and we could not isolate the desired product in acceptable purity. In the latter case, the reaction resulted in decomposition of triflate **1a**, and a significant amount of ethyl isobutyrate was recovered.

(7) An alternative pathway, enolization of **1** and fragmentation to provide a ketene intermediate, is inconsistent with a deuterium-labeling experiment. See the Supporting Information for details.